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**Psychosocial predictors of quality of life among South Africa adolescents receiving
antiretroviral therapy**

ABSTRACT

Minimal research has been conducted to understand the relationship between psychosocial factors, fatigue, and quality of life among adolescents living with HIV. We studied 134 South African adolescents receiving an antiretroviral therapy (ART) at community clinics to examine the relationship between fatigue, sleep disturbance, depression, anxiety, pain and quality of life. Participants reported low levels of fatigue, insomnia, distress and pain and non-problematic levels of quality of life (QOL). In the regression model, the linear combination of these variables explained 49% of the variance in quality of life. Insomnia, anxiety, and depression significantly predicted quality of life but fatigue and pain did not. Future research may address the relationship between self-reported adherence and QOL, possibly by examining the role of viral load (VL) as a mediating variable. Further research may also focus on non-adherent adolescents to understand the ways in which fatigue and other factors such as school functioning and social interaction influence QOL.

Key words: Quality of life, adolescents, fatigue, antiretroviral therapy

HIV prevalence among South Africans remains unacceptably high, with an estimated 12.7% of the general population and 5.6% of 15 to 24-year olds living with the virus. In 2012, 24% and 6% of new HIV infections in South Africa were among young women and men between the ages of 15 to 24, respectively [1]. The prevalence estimate for this age group was 7.1% (6.2%-8.1%) with females 8 times more likely than males to be infected. It is therefore apparent that girls are demographic group that is vulnerable to HIV. Behavioural factors that make adolescents susceptible to HIV infection include age-disparate sex, multiple partnerships, sex work and sexually exploited adolescent girls, transactional sex, early sexual debut, gaps in knowledge, and limited understanding of risk. Biological factors include the biological susceptibility of women, especially adolescent girls such as the HIV-susceptibility of the immature cervix, high HIV viral load (VL) among male partners, low prevalence of male circumcision, and harmful practices such as using substances to dry the vagina. Structural factors include gender inequality, unequal power dynamics, low secondary school attendance, barriers to accessing sexual and reproductive health services, orphanhood, child sexual abuse, and gender-based violence.

With the availability of ART, HIV has become a chronic rather than a life-threatening condition. South Africa has the largest number of persons enrolled in its ART programme in the world [2]. It is estimated that approximately 7.03 million South Africans were living with HIV in 2016.

There are several reasons that it is necessary to document and understand QOL among South African adolescents living with HIV. Firstly, with the advent of antiretroviral therapy, the longevity of persons living with HIV has increased to the extent that they may live well into their seventies and eighties. Evidence exists that starting ART immediately following diagnosis with HIV results in greater improvements in QOL compared to deferring treatment [3]. It has also been shown that improvement in QOL is associated with starting second line

ART, presumably following poor adherence to first line ART and consequent health deterioration [4]. To this extent, QOL is a necessary and important aspect of health to consider. Secondly, a substantial proportion of the South African adolescent population is currently living with HIV, indicating that QOL is a salient phenomenon for several thousand individuals. Indeed, it is estimated that in sub-Saharan Africa there are over 1.7 million adolescents living with HIV [5]. Thirdly, developmental differences mean that findings from the adult literature may not simply be applied to adolescents as their QOL experiences are unique and idiosyncratic. Fourthly, there is a need to understand the factors that contribute to QOL so that knowledge can be generated about where best to target interventions to ensure adolescents with HIV have optimal QOL given their life circumstances. To this extent, findings from this research may assist in identifying potential treatment targets for improving QOL and decreasing disease burden.

QOL among adolescents living with HIV

Previous psychosocial research on adolescents living with HIV has focused on mental health concerns, sexual risk behaviour, and the effect of educational programmes to reduce HIV incidence [6]. There appears to be minimal research on QOL among adolescents living with HIV. Using the search terms “adolescents”, “quality of life”, “HIV” and “Africa” we were able to find only two articles published in the last five years. Among Ugandan adolescents, receiving ART was associated with improved physical and mental health but poor communication with caregivers regarding sexuality or dissatisfaction with sexual and reproductive health services was associated with poor mental health [7]. Among Ghanaian adolescents who acquired HIV peri-natally more than two thirds were not virally suppressed and many reported barriers to treatment adherence, limited social support, concerns about disclosure and HIV-related stigma, limited resources, and low quality of life (QOL) [8]. One study among adolescents with HIV in the south-eastern United States found that health-

related QOL was correlated with life satisfaction and social-emotional strength and negatively correlated with negative affect and psychopathology symptoms [9].

QOL and Fatigue

Fatigue is a reduction in capacity for physical engagement in activities. The term “chronic fatigue” has come to refer to fatigue that is disproportionate to the nature of the task that is undertaken, persists for at least 1 month, and has no discernible cause [10].

Precipitating factors for chronic fatigue include psychological stress, dysfunction of the hypothalamus, pituitary, and adrenal glands, hormonal imbalance, infection, and suppression of the immune system [11]. Chronic fatigue has been observed in a range of illness conditions in adolescents such as rheumatoid arthritis[12], chronic pain[13], neurological conditions [14], multiple sclerosis [15], as well as in HIV in adults [16] and has been associated with low QOL (e.g. [17, 18]).

Persons living with HIV (PLWH) commonly experience elevated fatigue, which has been shown to be associated with poor engagement with treatment [19] thus yielding poor QOL. Low rates of ART adherence is a strong predictor of HIV-related infections and mortality. Fatigue may affect ART adherence, for example, due to oversleeping, impaired concentration, and a lack of physical energy to attend clinic appointments. For example, in a three-year longitudinal study of 128 PLWH, it was found that HIV-related fatigue was chronic and persistent in that spontaneous remission did not occur [20]. In addition, fatigue impeded work, family, and social life activities and was exacerbated by stress and depression. To our knowledge, no studies have shown a relationship between fatigue and QOL among adolescents living with HIV. In terms of the biopsychosocial model, it is likely and plausible that fatigue, as well as other related symptomatology such as sleep disturbance, pain, depression and anxiety are associated with QOL among PLWH.

QOL and insomnia: Insomnia has been shown to be associated with QOL in various populations such as cancer patients [21], patients with Type II diabetes [22]; and epilepsy [23].

One study of 206 patients admitted to a sleep disorder centre found that elevated levels of fatigue was associated with psychophysiological insomnia [24]. Yet, in this study daytime sleepiness was not predictive of fatigue and the two phenomena were therefore considered to be independent of each other. We found no studies on fatigue and insomnia among adolescents living with HIV, and to this extent the present investigation is the first of its kind.

QOL and distress: An intervention study to ameliorate symptoms of depression among PLWH showed that improvement in depression scores was associated with better physical and mental QOL, reduced fatigue intensity, as well as improvements in HIV symptoms [25]. Indeed, the symptom picture for major depression includes insomnia or hypersomnia nearly every day and fatigue or loss of energy nearly every day. Thus, in all likelihood, both insomnia and fatigue are likely to be common among depressed individuals.

Pain, an important dimension of QOL, is commonly reported among PLWH [26] and the virus may directly affect the musculoskeletal system [27]. Among 261 patients living with HIV in Brazil, more than half the sample reported moderate pain or severe pain, which was negatively associated with QOL[28]. Common pain diagnoses include multiple syndromes, degenerative disc disease or spinal stenosis, and neuropathy [29]. We were unable to find any studies on pain and QOL among adolescents living with HIV.

While the relationship between QOL, fatigue and psychological distress among adolescents living with HIV is largely unexplored, they have been shown to be highly correlated in other populations such as adults living with HIV [30, 31]; cardiac patients [32]; oncology patients [33]; and patients receiving treatment for multiple sclerosis [34]. A recent review found that employment, immunological status, presence of symptoms, depression,

social support and adherence to antiretroviral therapy were associated with health-related quality of life among individuals living with HIV [35]. Yet, as has been shown by a systematic review of reviews of QOL measurement instruments, concerns about valid measures of QOL abound [36]. In this study, we examined the relationship between fatigue, sleep disturbance, depression, anxiety, pain and QOL among adolescents receiving ART.

Methods

Participants

We recruited male and female adolescents, ages 11 to 18 years, enrolled in an ART programme at a community clinic and a district hospital in the Western Cape Province of South Africa. Inclusion criteria were competence in English or Afrikaans, the two most commonly-spoken languages in the province. Exclusion criteria were evidence of developmental delay, specifically difficulties with communication, or a diagnosis with a severe mental condition.

Procedure

Clinic staff informed eligible adolescent patients about the study during routine clinic visits. Those adolescents who indicated an interest in learning more about the study were referred to a research assistant in a private room at the clinic, where the study was explained in greater detail and the patient was invited to participate. The research assistant followed the established procedures for gaining informed consent. We received ethics clearance for a parental waiver of consent, given that most of our participants attended their consultations alone. All participants were clinician referred.

The questionnaire battery was presented to participants in English or Afrikaans, depending on participant preference. The battery was self-administered by participants. If they indicated difficulty in understanding specific questions, they were helped by the research assistant. The translation of the Chalder Fatigue Questionnaire (CFQ) and the Revised Child

Anxiety and Depression Scale (RCADS) was conducted by a bilingual post-graduate psychology student and the Afrikaans version was then checked by one of the authors (BC). However, we did not conduct a back-translation of these measures.

Measures

QOL: Pediatric QOL Inventory (PedsQLTM4.0 short form SF15) [37] was used to measure QOL among the sample. The PedsQL is a 23-item questionnaire that is appropriate for use among individuals up to the age of 18. The instrument has four subscales, namely, physical functioning, emotional functioning, social functioning, and school functioning. It yields a physical health (8 items), psychosocial health (15 items), and total QOL summary score (23 items). The PedsQL has good psychometric properties including alpha reliability of 0.90 for the children's version. It has been shown to validly distinguish between healthy children and those with a health condition, as well as disease severity within a chronic health condition.

Fatigue: We used the CFQ [38] to assess fatigue. The CFQ is a four-point Likert-type scale with 11 items that assesses the severity of both mental and physical fatigue within the past month. The CFQ has been used among populations with a range of health conditions [39], including adolescents with fatigue [40, 41]. We used the Likert method of scoring the scale, i.e. we calculated the total score out of a possible 33, with a score of > 18 indicating elevated fatigue [42].

Insomnia: We used the 8 item Athens Insomnia Scale (AIS) to assess insomnia. The AIS is a four-item Likert-type scale that enquires about sleep problems that occur for the respondent three times per week during the previous month. The items assess sleep induction, awakenings during the night, final awakening, sleep duration, sleep quality, well-being, functioning capacity, and daytime sleepiness. The AIS has been shown to have high internal consistency, with an alpha coefficient of 0.90 [43].

Depression: The RCADS contains a 10-item depression subscale, designed to assess mood in children ages 7-18[44]. Items pertain to feeling sad or empty, anhedonia, sleep and appetite disturbance, having no energy and feeling tired, feelings of worthlessness, and feeling restless.

Anxiety: The RCADS also contains 6 items that pertain to symptoms of anxiety, i.e. worrying about things, worrying about bad things happening, and thinking about death. Both the depression and anxiety subscales of the RCADS have been shown to have high validity and reliability in both clinical and nonclinical populations [44–47]. For the statistical analysis, we converted the raw scores on the RCADS into a T-score with a mean of 50 and standard deviation of 10 [48]. On both the depression and anxiety subscales of the RCADS, a converted score of 65 indicates possible clinical significance and a converted score of 70 indicates probable clinical significance [49].

Pain: To assess pain, we used a Visual Analogue Pain Scale (VAPS). Participants were asked to mark on a line the severity of their pain from no pain at all to pain as bad as possible. A VAPS has often been used to measure the intensity or frequency of pain. It is assumed that the intensity of pain felt by a participant ranges from none to an extreme amount on a continuous spectrum rather than taking discrete jumps as would be indicated on a Likert-type scale [50]. A cut-point of 4 was used to distinguish between clinically significant and non-significant pain.

Cronbach's alpha of all the assessment instruments exceeded 0.80, indicating very high internal consistency of the scales. Means, standard deviations and minimum and maximum scores of the sample on the various measures are presented in Table 2.

Ethical considerations

We obtained ethics approval for this study from the Stellenbosch University Research Ethics Committee and the Western Cape Department of Health. Participants were asked to complete an informed consent form and were assured of confidentiality of their data.

Data analysis

We used SPSS v24 to analyse the data. The analysis included calculating Cronbach's alpha to determine the internal consistency of the scales used and descriptive statistics to describe the demographic variables. We used Pearson's r to calculate bivariate correlations among the variables and linear regression analysis to determine the linear contribution of the predictor variables, i.e. fatigue, insomnia, anxiety, depression and pain, on the criterion variable, i.e. QOL. To determine gender differences among the variables, we conducted t -tests with a Bonferroni correction. The sample size was adequate using a rule of thumb of 15 participants per predictor variable.

Results*Description of the sample*

As shown in Table 1, we recruited 134 adolescents (78 female and 56 male) whose mean age was 14.33 years. Twenty-four (17.9%) of the participants endorsed the "coloured" racial group and 110 (82.1%) identified as Black. All participants except one were in high school and one was employed part-time. More than half the sample identified as Christians. *QOL*: As can be seen in Table 2, the sample reported on average high QOL on the physical, emotional, social and school QOL domains, as well as the total score for the measure. The total mean score on the PedsQL was 24.56 (SD=13.71), which was significantly lower than the cut-point of 70 indicating problematic levels of QOL [51]. Females reported significantly lower QOL than males.

Fatigue: The mean score on the CFQ was 14.89 (SD=3.82) out of a possible total score of 33. The mean score was significantly lower ($t=-9.42$; $df=133$; $p<0.00$) than the commonly used cut-point of 18 [52], which indicates that the average fatigue level of the sample was within the normal range. Clinically significant fatigue on the CFQ is considered to be 19 and above [52]. There were no significant differences between males and females on the CFQ.

Insomnia: The mean score on the AIS was 3.92 (SD=3.38) out of a possible total score of 24. The mean score was significantly lower ($t=-10.52$; $df=133$; $p=0.00$) than the commonly used cut-point of 7 [53], which indicates sleep problems that occur out of the normal range. Clinically significant insomnia on the AIS is considered to be 7 and above.

Depression: The mean converted T-score on the RCADS Depression subscale was 44.70 (SD=12.33). The mean score was significantly lower ($t=-19.05$; $df=133$; $p=0.00$) than the threshold of 65, indicating the probability of clinically significant depression, and only 5.2% scored in the clinically significant range. On average our sample represented non-depressed adolescents.

Anxiety: The mean converted T-score on the RCADS Anxiety subscale was 43.9 (SD=12.78). The mean score was significantly lower ($t=-19.11$; $df=133$; $p=0.00$) than the threshold of 65, indicating the probability of clinically significant anxiety, and only 9.0% of the sample scored in the clinically significant range. On average our sample represented non-anxious adolescents.

Pain: The mean score on the VAPS was 0.82 (SD=1.82) out of a possible total score of 7. The mean score was significantly lower ($t=-19.87$; $df=133$; $p=0.00$) than the threshold of 4 on the VAPS, indicating at least mild pain [54].

Bivariate correlations

Table 3 presents the correlation coefficients among the variables of interest. QOL highly and significantly correlated with insomnia, depression, anxiety, and fatigue but not pain.

We found significant correlations between depression, insomnia and fatigue, and between anxiety and insomnia. Scores on the pain measure were not found to be associated with any of the variables included.

Results of the regression analysis

The various regression diagnostics, including the Cook's and Mahalanobis distances, and variance inflation factors were within the acceptable range for regression analysis. The data were normally distributed making it possible to conduct a regression analysis. Table 4 presents the regression model summary with QOL as the criterion variable. The linear combination of the predictors, namely, insomnia, fatigue, anxiety and depression explained 49% of the variance in QOL, a large effect size [55]. Table 5 shows that insomnia, anxiety and depression were unique significant predictors of QOL. Neither fatigue nor pain emerged as significant predictors of QOL.

Discussion

On average participants in this study reported levels of insomnia, fatigue, anxiety, depression and pain that fell in the normal ranges on the instruments that assessed these variables. This finding is positive in that it appears that many members of the sample experienced non-clinical levels of sleep disturbance, fatigue and psychosocial distress in comparison with the commonly used cut-points of the measures that assessed these constructs.

In previous research, symptoms of depression and anxiety have been shown to be common among adolescents with HIV [56–58]. However, very few members of our sample scored in the elevated range on the depression and anxiety measures. Similarly, QOL was

within the normal range. These findings are surprising it would be assumed that adolescents living with HIV, especially those of poorer socio-economic backgrounds, would experience lower QOL than those from middle class backgrounds. That our data refute this assumption is certainly a novel finding and provides some evidence that living with HIV need not result in poor QOL or excessive fatigue, at least in a clinic-attending population.

The linear combination of our predictor variables explained just under 50% of the variance in QOL, which is a large effect size. Insomnia, anxiety, and depression were significant predictors in the model. Even though scores on the instruments measuring these variables fell in the non-clinical range, they were still robustly predictive of poor QOL.

However, we were surprised that neither fatigue nor pain emerged as significant predictors. Our data contradict that of previous research indicating that, at least for some, fatigue is predictive of QOL [59]. The level of pain reported among our sample was minimal, presumably accounting for the fact that it did not emerge as a significant factor in the model.

By identifying which of several biopsychosocial factors investigated contribute most substantially to QOL in this population, our findings suggest what might be most important to address, both in terms of research and in clinical practice. Our findings are not entirely consistent with findings in the adult HIV literature, illustrating the importance of undertaking this research with the adolescent population. By virtue of their developmental stage and its associated factors, for example, being in school rather than economically active, and being dependent upon others rather than autonomous, QOL may be maximised by different processes. It was somewhat surprising but also reassuring to find non-problematic levels of QOL among our participants. This finding suggests that adolescents receiving ART may live satisfying lives and may not be unduly limited by physical or mental health complaints.

The strengths of the study include the fact that this is among only a few studies to examine QOL among adolescents living with HIV in Africa and as far as we know the only

one in South Africa. Also, we recruited adolescents who were enrolled on a state-sponsored anti-retroviral therapy programme and were actively receiving HIV-related care.

We have identified some limitations to the study. First, this was a cross-sectional study, which imposes limitations on any claims about causal relationships among the variables. Second, we did not report data on VL. VL is highly influenced by ART adherence levels [60] and predicts HIV-related symptoms [61] and thus health-related QOL. At the clinical sites where the study was conducted, the testing and capturing of VL was inconsistent and thus these data were not usable. It is possible that the sample consisted of highly adherent individuals, as they were recruited at the clinics where they were seeking treatment. This could explain why their QOL was within normal limits. Third, it is possible that acceptance of the HIV diagnosis may increase with time, resulting in the natural amelioration of symptoms of depression and anxiety. However, we did not collect data on time since diagnosis and therefore could not test this hypothesis.

Future research may address the relationship between medication adherence and QOL, possibly by examining the role of fatigue as a mediating variable. For example, oversleeping, impaired concentration, and a lack of physical energy to attend clinic appointments are expressions of fatigue which may affect ART adherence. Nonetheless, the study shows a robust relationship between sleep disturbance, psychosocial factors such as depression and anxiety and QOL among our sample. Further research may focus on non-adherent adolescents to understand the ways in which fatigue and other factors such as school functioning and social interaction influence QOL. For example, Loades, Coetzee, Du Toit and Kagee (2018) found that South African adolescents enrolled on the national ART programme reported impaired social interaction, poor concentration and memory, and low levels of energy which influenced their ability to function at school[62].

The cognitive and behavioural responses to fatigue in this population have not been investigated, and therefore, further research is needed to explore these factors and the appropriateness of a cognitive behavioural model in conceptualising fatigue among adolescents with HIV. Given the criticisms of research into cognitive therapy to ameliorate symptoms of chronic fatigue, this line of investigation may be especially timely. Considering the overlap between mood disturbance and fatigue, and the fact that fatigue forms part of the symptom picture for major depressive disorder, research into specific interventions such as behavioural activation and exercise scheduling is also indicated.

Conclusion

In the context of public health systems in the global South that are increasingly resource-constrained, it is appropriate to consider task-shifting of clinical functions previously provided by highly trained psychologists and psychiatrists to lower level nurses, peer counsellors, and patient advocates. Evidence for the effectiveness of such interventions would be of considerable use to policy-makers concerned with the psychosocial well-being of adolescents living with HIV.

Compliance with Ethical Standards

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Conflict of Interest: Dr. Kagee declares that he has no conflict of interest. Dr. Coetzee declares that she has no conflict of interest. Ms. Du Toit declares that she has no conflict of interest. Dr. Loades declares that she has no conflict of interest.

Ethical approval: All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent: Informed consent was obtained from all individual participants included in the study.

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Table 1. Sample characteristics

		Frequency	(%)	M	SD
Age (in years)				14.33	1.99
Gender	Female	78	58.2		
	Male	56	41.8		
Ethnicity	Coloured	24	17.9		
	Black	110	82.1		
Social Class	Lower	94	70.1		
	Working	38	28.4		
	Middle	2	1.5		
Religion	Christian	75	56.0		
	Protestant	1	0.7		
	Catholic	1	0.7		
	Pentacostal	1	0.7		
	Methodist	2	1.5		

Table 2: Descriptive statistics

	Min and max scores	Mean	SD
PedsQL Physical	0-32	7.07	5.70
PedsQL Emotional	0-20	6.97	4.07
PedsQL Social	0-20	3.34	4.41
PedsQL School	0-20	7.14	3.71
PedsQL Total	0-92	24.56	13.71
Chalder Fatigue Scale	0-33	14.89	3.82
Athens Insomnia Scale	0-24	3.92	3.38
RCADS-Depression	0-30		
RCADS-Anxiety	0-18		
Visual Analogue Pain Scale	1-7	0.86	1.82

Table 3: Bivariate correlation matrix of variables

	(1)	(2)	(3)	(4)	(5)	(6)
(1) QOL	1					
(2) Insomnia	0.57*	1				
(3) Depression	0.60*	0.42*	1			
(4) Anxiety	0.43*	0.24*	0.54*	1		
(5) Fatigue	0.49*	0.56*	0.46*	0.16	1	
(6) Pain	-0.02	0.2	-0.2	-0.06	0.13	1

Table 4: Model summary with QOL as the criterion variable

Outcome	Model	Predictors	<i>R</i>	<i>R</i> square	Adj <i>R</i> square	<i>R</i> square change	<i>F</i> ratio	<i>F</i> change
Peds QOL	1	Constant, Insomnia (Athens)	0.57	0.32	0.31	0.32	62.01	0.00
	2	Constant, Insomnia, Fatigue	0.60	0.37	0.36	0.05	37.58	0.00
	3	Constant, Insomnia, Fatigue, Anxiety, Depression	0.71	0.51	0.49	0.14	33.16	0.00
	4	Constant, Insomnia, Fatigue, Anxiety, Depression, Pain	0.71	0.51	0.49	0.00	26.43	0.605

Table 5: Predictors of quality of life

Model	<u>Unstandardized Coefficients</u>		<u>Standardized</u>	<i>t</i>	<i>p</i>
	<i>B</i>	<i>Standard Error</i>	<u>Coefficients</u>		
Constant	-11.23	4.52			0.01
Insomnia	1.27	0.31	0.31	-2.49	0.00
Fatigue	0.54	0.29	0.15	4.09	0.06
Anxiety	0.16	0.08	0.15	1.87	0.04
Depression	0.35	0.09	0.32	2.03	0.00
Pain	-0.25	0.47	-0.03	-0.52	0.61